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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/809,827	03/16/2001	Christen M. Anderson	660088.420D6	7995

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EXAMINER	
SCHNIZER, HOLLY G	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 02/25/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/809,827	ANDERSON ET AL.	
	Examiner	Art Unit	
	Holly Schnizer	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 November 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *42,43,47-57 and 113* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *42,43,47-57 and 113* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 May 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restriction

In the response filed November 25, 2003, Applicants affirmed the election of Group IV, claims 42-44 and 47-57. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Therefore, the restriction is made FINAL.

Status of the Claims

Claims 1-41, 44-46, and 58-112 were cancelled. Claim 113 was added. Therefore, Claims 42-43, 47-57, and 113 are currently pending and have been examined on the merits below.

Objection for Sequence Compliance Withdrawn

The objection to the disclosure for lack of sequence identifiers in Figures 1-2 is withdrawn in light of the amendment to the Brief Description of the drawings adding the identifiers.

Rejections Withdrawn

Claim Rejections - 35 USC § 112--Withdrawn

The rejections of Claim 43-45 under 35 U.S.C. 112, second paragraph as unclear as to the scope of the claim in light of dependent Claims 44-45 are withdrawn in light of the amendment to the claim and cancellation of Claims 44-45.

Claim Rejections - 35 USC § 102--Withdrawn

The rejection of Claims 43-45 under 35 U.S.C. 102(a) as being anticipated by Marzo et al. (Science (Sept. 25, 1998) 281(5385): 2027-2031 ; ref. CG in IDS of Paper No. 6) is withdrawn in light of the cancellation of Claims 44-45 and the amendment to Claim 43. The ANT polypeptides of Marzo et al. are a recombinantly produced ANT2 fragment (Fig. 4B) and a purified ANT from rat myocardium (see Fig. Legend 4C). ANT1 from rat is only 94.4% identical to SEQ ID NO:31 (see sequence alignment attached to this Office Action) and therefore is not considered a variant having at least 95% identity of SEQ ID NO:31.

The rejection of Claims 43-45 under 35 U.S.C. 102(b) as being anticipated by Adrian et al. (Mol. Cell. Biol. (1986) 6(2): 626-634; ref. AH of IDS of Paper No. 6) is withdrawn in light of the amendment to Claim 43 and cancellation of Claims 44-45. It appears that yeast ANT proteins do not have at least 95% identity to SEQ ID NO:31 and therefore are not considered variants having at least 95% identity to SEQ ID NO:31.

The rejection of Claims 43-44 under 35 U.S.C. 102(e) as being anticipated by Wallace et al. (U.S. Patent No. 6,013,858) is withdrawn in light of the amendment to Claim 43 and cancellation of Claim 44.

Claim Rejections - 35 USC § 103-Withdrawn

The rejection of Claims 42-44, 47-50, 52-55, and 57 under 35 U.S.C. 103(a) as being unpatentable over Adrian et al. (Mol. Cell. Biol. (1986) 6(2): 626-634; ref. AH of IDS of Paper No. 6) in view of Fiore et al. (Biochimie (Feb. 1998) 80: 137-150; ref. BG

of IDS of Paper No. 6) and Marzo et al. (Science (Sept. 1998) 281 : 2027-2031) is withdrawn in light of Applicants arguments and the Anderson Declaration filed November 25, 2003 and two newly cited references; Hatanaka et al. (Biol. Pharm. Bull. (2001) 24(6): 595-599) and Heimpel et al. (J. Biol. Chem. (2001) 276(15): 11499-11506). Hatanaka et al. disclose expression of human ANT1 in yeast. However, Hatanaka et al. teach that the N-terminal region of the human ANT polypeptide had to be replaced with the yeast sequence in order to achieve significant expression. Therefore, Hatanaka et al. provide evidence that one of ordinary skill in the art would not have achieved success by combining the teachings of Adrian et al., Fiore et al., and Marzo et al. Heimpel et al. disclose the expression of an ANT from N. crassa in E. coli. Heimpel et al. state that yeast AAC2 and mammalian AAC (also referred to as ANT) are not expressed at significant levels in E. coli and that there is no evidence that the proteins are incorporated into E. coli membranes (p. 11504, Col. 1). Heimpel et al. also discuss the "challenge" of reconstitution of AAC from inclusion bodies and the modification they had to make for successful reconstitution from inclusion bodies (p. 11504, Col. 2). Thus, Heimpel et al. provides additional evidence of failure to express mammalian ANT in E. coli. While both Hatanaka et al. and Heimpel et al. are post-filing references, they show that even after the filing date of the present invention, heterologous expression of mammalian ANT was not routine.

The rejection of Claims 51 and 56 under 35 U.S.C. 103(a) as being unpatentable over Adrian et al., Fiore et al., and Marzo et al., as applied to claims 42-44, 47-50, 52-55, and 57 above, and further in view of Rosenberg (Protein Analysis and Purification:

Benchtop Techniques (1996) Birkhauser, Boston, pp. 335-347) is withdrawn for the same reasons given immediately above for the withdrawal of the obviousness rejection. In light of the references in the art, it appears that recombinant expression of mammalian ANT polypeptides was not routine at the time of the invention.

New Rejections

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 42, 43, and 113 are rejected under 35 U.S.C. 102(b) as being anticipated by Neckelmann et al. (Proc. Natl. Acad. Sci. (1987) Vol.84, pp. 7580-7584).

Neckelmann et al. teach the isolation of a cDNA clone encoding ANT1 from human skeletal muscle (p. 7580-7581). The DNA and encoded protein sequences of the disclosed ANT polynucleotide and polypeptide are disclosed on page 7582. The polypeptide sequence of Neckelmann et al. is 98.3% identical to SEQ ID NO:31 (see sequence alignment attached to this Office Action). Neckelmann et al. teaches the in vitro transcription and translation of the ANT polypeptide (Fig. 4). This polypeptide is considered isolated as compared to the polypeptide in nature. Moreover, the polypeptide is further isolated on a polyacrylamide gel (Fig. 4). While the protein

disclosed in Neckelmann et al. is not made by the same process as the protein presently claimed, the protein of Neckelmann et al. has the same sequence as the claimed protein. Therefore, the protein of Neckelmann et al. is considered patentably indistinguishable from the protein of Claim 42 and the variant of Claim 43 (see MPEP 2113 which indicates that product-by–process claims are not limited by the steps unless the steps change the characteristics of the product claimed). In addition, Neckelson et al. meets the limitations of Claim 113 because the protein of Neckelmann et al. contains more than 30 contiguous amino acids identical to SEQ ID NO: 31 and therefore the protein disclosed therein is considered a fragment comprising at least 30 amino acid residues set forth in SEQ ID NO:31.

Claim 113 is rejected under 35 U.S.C. 102(a) as being anticipated by Marzo et al. (Science(Sept. 1998) 281: 2027-2031).

Marzo et al. is considered to teach a fragment of an isolated recombinant ANT1 polypeptide wherein the fragment comprises at least 30 contiguous amino acid residues of the sequence set forth in SEQ ID NO:31. Marzo et al. discloses the expression of residues 105-156 of human ANT2 (see Fig. 4B). The expression results in a functional fragment as evidenced by its binding of Bax (Fig. 4B). A comparison of the ANT1 isoform and ANT2 isoform amino acid sequences shows that the two isoforms have identical sequences between residues 108-146 (contained within the fragment disclosed in Marzo et al.; a copy of the ANT1 and ANT2 sequences as disclosed in the present Application is attached to this Office Action for convenience in comparing the

sequences). Therefore, the fragment disclosed in Marzo et al. has 39 contiguous amino acid residues of SEQ ID NO:31 and is considered to meet the limitation that the fragment must have at least 30 contiguous amino acids of SEQ ID NO:31. The examiner notes that the present claim does not require the fragment to be isolated.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 42 and 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rojo and Walliman (Biochim. Biophys. Acta (1994) 1187: 360-367), Marzo et al. (Science (Sept. 1998) 281: 2027-2031) and Kramer (Methods in Enzymol. (1986) 125:

610-618) in view of Neckelmann et al. (Proc. Natl. Acad. Sci. (1987) 84: 7580-7584), and Fiore et al. (Biochimie (Feb. 1998) 80: 137-150).

The examiner notes that while the claims are drawn to a product by process, they have been considered as to whether or not the claimed product is patentably distinguishable over the products of the prior art (see MPEP 2113; product by process claims are not limited by the process steps). The product claimed is considered to be an adenine nucleotide translocator (ANT) polypeptide comprising an amino acid sequence that is at least 95% identical to the sequence set forth in SEQ ID NO:31.

Rojo and Walliman disclose the purification of ANT from bovine heart, chicken heart, and rat heart, brain, liver, and kidney (p. 365, Col. 2, last paragraph) and indicate that the purification method disclosed could be used for purification of ANT from other sources (p. 367, Col. 1, last paragraph). Rojo and Williams provide evidence that the isolation and purification of adenine nucleotide translocators from nature was "simple and rapid" at the time of the invention (see p. 361, Col. 1, line 9).

Marzo et al. describe the isolation of ANT2 from rat myocardium.

Kramer disclose a protocol for the isolation of ANT from bovine heart tissue.

Rojo and Walliman, Marzo et al., and Kramer provide evidence that purification of ANT polypeptides was routine in the art at the time of the invention. However, Rojo and Walliman, Marzo et al., and Kramer do not specifically teach the purification of a human ANT polypeptides. A search of the sequence databases indicates that bovine, rat, and chicken ANT polypeptides are less than 95% identical to SEQ ID NO: 31. Therefore,

the proteins disclosed in Rojo and Walliman, Marzo et al., and Kramer would not be expected to be encompassed by the claims.

Neckelmann et al. disclose a sequence for ANT1 isolated from skeletal muscle that is 98.4% identical to SEQ ID NO:31 of the present invention (see sequence alignment attached to this Office Action). Neckelman et al. state that the skeletal muscle ANT is expressed in heart, kidney, liver, skeletal muscle, and HeLa cells (see p. 7580, Col. 2, lines 27-28). Therefore, Neckelmann et al. provides evidence that one of ordinary skill in the art would know what tissues could be used for the isolation of human ANT1.

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to isolate human ANT1 having the sequences disclosed in Neckelson et al. using routine isolation procedures such as those taught in Rojo and Wallimann, Marzo et al., and/or Kramer. In making the present obviousness rejection, the examiner has considered applicants arguments and the Anderson Declaration filed November 25, 2003. However, neither the arguments nor the Declaration provide any evidence that one of ordinary skill would have expected that human ANT1 could not be isolated by prior art methods. In fact, Rojo and Wallimann show isolation of ANT from a variety of species (bovine, chicken, rat) and from a variety of tissues (heart, brain, liver, kidney) and suggest that the purification procedure disclosed therein could be used for other sources of ANT not tested therein (p. 367, Col. 1, last paragraph of Discussion). Thus, absent evidence that human ANT could not be isolated by the routine procedures known in the art for isolating other species and in the presence of Rojo and Walliiman

who teach an ANT purification procedure that they indicate is appropriate for isolating ANT from a variety of species, it appears that one of ordinary skill in the art at the time of the invention would have had a reasonable expectation of isolating human ANT1 using the routine isolation procedures known in the art and evidenced by references such as Rojo and Walliman, Marzo et al., and Kramer. One of ordinary skill in the art would have been motivated to isolate human ANT1 in order to characterize the protein. Characterization of human ANT proteins is essential to the development of diagnostic and treatment tools because as taught in Fiore et al. (p. 146, Col. 2), these proteins have a central role in cellular energy metabolism and it is likely that dysfunction of these proteins is involved in mitochondrial disorders. In this respect, characterization of ANT1 would be especially desirable given the knowledge that there is increased expression of ANT1 in the muscle of patients with myoclonic epilepsy associated with ragged-red fibers and myopathy, encephalopathy, lactic acidosis and stroke-like episodes (see Fiore et al. p. 146, Col. 2, 2nd paragraph of 2nd full paragraph).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 47-57 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to

one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 47-57 are all directed to recombinant ANT1 proteins. Claims 47-51, and 57 include the limitation that the ANT1 polypeptide is "human". Claims 52-57 include the limitation that the claims are "animal". However, the present Specification only provides one species (the human ANT1 of SEQ ID NO:31) and does not include any identifying characteristics of an ANT sequence that is "human" or "animal" so that one of ordinary skill in the art could recognize the source of the protein based on its sequence. The examiner notes that the claims are product by process claims wherein the claimed proteins are made by recombinant expression and do not require that the protein be isolated from a particular source in nature. Thus, the scope of the claims includes not only ANT1 sequences found in nature but those made in vitro. Thus, when is a sequence considered "human" or "animal"? How many and which amino acids would have to be changed for the disclosed sequence to be considered non-human or non-animal? At a time when recombinant expression and mutagenesis are routine, some type of characteristic feature of human ANT sequences would be required for one of skill in the art to be able to distinguish a human sequence from non-human and animal sequences from non-animal. For example, if an ANT protein was heterologously expressed, what sequences of all the sequences that are at least 95% identical to SEQ ID NO:33 would be considered "human". Therefore, given that the Specification provides only one species of the genus, that the claims are drawn to proteins made by recombinant expression which can produce any protein sequence, and that all of the

human and animal ANT sequences are not presently known, the present Specification has not provided sufficient written description as to what sequences are considered human or animal.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 47-51 and 56-57 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The scope of independent claims 47, 51, and 56 is unclear because the claims are drawn to "human" ANT1 sequences (see first line of Claims 47 and 51) or "animal" ANT1 (see Claim 56, line 1) yet the claims are broadly limited to any ANT1 sequence (see Claim 56) or any ANT1 sequence at least 95% identical to SEQ ID NO:31. Thus, the claims are confusing as to whether they encompass only "human" (for Claims 47 and 51) or "animal" (for Claim 56) sequences or whether they are broader and encompass any ANT1 sequence (for Claim 56) or any ANT1 sequence 95% identical to SEQ ID NO:31 (in the case of Claims 47 and 51). Claims 48-50 and 57 are rejected because they depend from the independent claims discussed above but do not correct their deficiencies. Clarification is required.

Conclusions

No Claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Holly Schnizer whose telephone number is (571) 272-0958. The examiner can normally be reached on Tuesday, Thursday, and Friday from 8 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (571) 272-0951. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Holly Schnizer
February 15, 2004

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